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Association of the Delta SARS-CoV-2 variant with 28-day hospital mortality between December 2020 and September 2021

Running title: Association of Delta VOC with 28-day hospital mortality

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Dear Editor,

The spreading of SARS-CoV-2 variants of concern (VOCs) have been associated with a surge of COVID-19 cases and the burden of the healthcare systems worldwide (https://www.who.int/en/activities/tracking-SARS-CoV-2-variants). In response, the Reference Centre for the Network of COVID-19 Genomic Surveillance in the Canary Islands (Spain) was established in our laboratories by the regional public health system. We tracked the early emergence of the Alpha variant (Alcoba-Florez *et al.*, 2021) and described the introduction and dynamics of four VOCs in the region from December 2020 to September 2021 (Ciuffreda *et al.*, 2022). There are major concerns that some VOCs may cause increased disease severity. In this journal, Strålin and colleagues have reported higher rates of hospitalization, severe illness and death among those infected with the Alpha variant (B.1.1.7) compared to non-VOC lineages (Strålin *et al.*, 2022). Since the Delta (B.1.617.2) variant has been associated with even higher disease severity compared with Alpha (B.1.1.7) (Twohig *et al.*, 2022), here we aimed to retrospectively assess the association between infection by the two major VOCs circulating in the Canary Islands (Spain) archipelago during the period and 28-day mortality among a cohort of hospitalized patients.

The study was conducted at the University Hospital Nuestra Señora de Candelaria (HUNSC) (Santa Cruz de Tenerife, Spain). The institutional review board approved the study (approval CHUNSC_2020_24). As previously described (Ciuffreda *et al.*, 2022), nasopharyngeal swab samples were collected in the Canary Islands archipelago from December 2020 to September 2021. Of the 8,224 samples analysed throughout the study period, clinical and patient data were available for only a subset of 5,544 samples, out of which 532 samples were collected from hospitalized patients in our centre. To exclude samples from patients who attended the hospital for causes unrelated to COVID-19 or who had a nosocomial SARS-CoV-2 infection, we included in the analysis only those patients who were hospitalized between one and 21 days from symptoms onset. Sample collection, genome sequencing and lineage assignment are briefly described in the supplementary material and further detailed elsewhere (Ciuffreda *et al.*, 2022). Logistic and Cox proportional hazard regression models adjusting for patient age, sex, days of hospital stay, and personal history of comorbidities were used to assess whether infection by VOCs in hospitalized patients was associated with 28-day hospital mortality.

Clinical and demographic information of the study population is included in **Table S1**. A total of 423 genome sequences were identified as Alpha (B.1.1.7) or Delta (B.1.617.2 and sub-lineages). Delta was found in a slightly lower proportion of elderly (>50 years) patients (59.2%) compared with Alpha (65.9%), probably reflecting a larger proportion of vaccinated individuals in that age range when Delta was circulating (May to September 2021) (Ciuffreda *et al.*, 2022). Despite this, and the higher proportion of vaccination when Delta circulated (50-75% of the population with $\geq$1 dose

between July and September 2021) than when Alpha circulated (1-35% of the population with ≥1 dose between January and June 2021) (https://www.sanidad.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov/pbiVacunacion.htm), infection by Delta lineages was associated with higher 28-day hospital mortality compared to that of Alpha irrespective of the model (**Table 1**). Age and male sex were also consistent predictors of higher 28-day hospital mortality.

As a limitation, we did not have access to the vaccination status of the patients. This is mainly due to the lack of a centralized system in Spain where patient vaccination status is stored and to the large proportion of the floating or non-resident population in the islands, such as holidaymakers, nomadic workers, or migrants, who lack health status information in the local databases. We aimed to mitigate the bias caused by this by focusing on hospitalized patients, under the idea that their vaccination level was less relevant for disease severity once the patient was hospitalized. Taken together, hospitalized cases with Delta or any of its sub-lineages were associated with higher mortality compared to those with Alpha, adding to the evidence supporting that Delta was more severe than pre-existent SARS-CoV-2 variants (Bager *et al.*, 2021; Freire Rodrigues *et al.*, 2022; Twohig *et al.*, 2022).

Table 1. Association results of SARS-CoV-2 VOCs infections with 28-day mortality among hospitalized patients.

	Logistic regression		Cox regression	
	Odds Ratio (95% CI)	***p*-value**	**Hazard Ratio (95% CI)**	***p*-value**
Lineage (Delta (B.1.617.2 and sublineages) *vs.* Alpha (B.1.1.7))	2.24 (1.11-4.78)	0.029	2.28 (1.18-4.39)	0.014
Age (years old)	1.06 (1.03-1.09)	4.68×10^{-6}	1.05 (1.03-1.07)	1.20×10^{-6}
Sex (male)	2.45 (1.17-5.40)	0.020	2.03 (1.06-3.88)	0.031
Length of hospital stay (days)	0.98 (0.95-1.01)	0.415	0.93 (0.89-0.97)	2.64×10^{-4}
Comorbidities*	1.65 (0.69-4.21)	0.271	1.55 (0.66-3.60)	0.309

CI, confidence interval.
*Detailed in Table S1.

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Author contributions

CF conceived the idea, the experimental design and supervised the project. LC, JAF, JMLS, HRP, HGC, AIC, RGM, and DGMA conducted the sequencing experiments. JAF, HGC, ODG, and DGMA collected patient data. LC, JMLS, AVF, and CF performed the analysis and interpreted the results. CF obtained the funding. CF and LC drafted the first version of the manuscript and prepared the tables. All authors contributed to manuscript revision and read and approved the submitted version.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data Availability Statement

Generated consensus sequences were deposited to GISAID.

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